REMARKS

Claims 4 is pending in the instant application. Claim 4 has been rejected. No new matter has been added by this amendment. Reconsideration is respectfully requested in light of the following remarks.

I. Withdrawn objections

Applicants are pleased to acknowledge that the objection to the title has been withdrawn.

II. Rejection of Claim 4 Under 35 U.S.C. §112

The rejection of claim 4 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention has been maintained. The applicants respectfully traverse this rejection.

The Examiner suggests that a prophetic procedure for treating Alzheimer's disease with an agent that inhibits the processing of amyloid precursor protein into amyloid β peptides in combination with *in vitro* experiments with NT2N cells is not adequate guidance, but merely an invitation to the artisan to use the current invention as a starting point for further experimentation. The Examiner further suggests that the present invention is unpredictable and complex such that the skilled artisan may not necessarily inhibit the processing of amyloid precursor protein into amyloid β peptides in patients with Alzheimer's disease by administering an agent that decreases

processing. Moreover, the Examiner suggests that the NT2N model system is a predictable system used to study APP processing in neurons, but is not an art recognized model system for Alzheimer's disease, thus the skilled artisan would not predict from the guidance in the specification that an agent that decreases amyloid precursor protein processing in the NT2N model system would necessarily decrease amyloid precursor protein processing in a patient.

At the onset, Applicants respectfully disagree with the Examiners interpretation of claim 4. Claim 4 is directed to a method of inhibiting a biological endpoint (*i.e.*, processing of amyloid precursor protein into amyloid β peptides) which is associated with one sign (*i.e.*, neuritic plaques and vascular deposits) of Alzheimer's disease and not a method of preventing or treating Alzheimer's disease.

MPEP 2164.02 states that an *in vitro* or *in vivo* animal model example in the specification, in effect, constitutes a "working example" if that example "correlates" with the disclosed or claimed method of the invention.

As acknowledged by the Examiner, the NT2N model system is a recognized model for studying APP processing in neurons. Accordingly, Applicants have provided an *in vitro* model example which correlates with the disclosed or claimed method of the invention. Applicants believe that their assertion that the claimed invention is useful in inhibiting a sign (*i.e.*, amyloid β peptides found in neuritic plaques and vascular deposits) of a disease in a patient (*e.g.*, Alzheimer's disease) would be considered credible and predictable by a person of ordinary skill in the art on the basis of using the NT2N cells to identify an

agent which modulates the levels of amyloid β peptides formed in the endoplasmic reticulum of said cells.

The Examiner further suggests that the skilled artisan must resort to trial and error experimentation to determine the optimal dose, duration, and mode of administration of all possible agents as the specification provides no guidance regarding what sort of agents should be screened for inhibiting the processing of amyloid precursor protein.

MPEP 2164.01 states the test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. A patent need not teach, and preferably omits, what is well known in the art. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. Denied*, 480 U.S. 947 (1987); and *Lindemann Maschinenfabrick GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984).

As the secretase enzymes are proteases, the skilled artisan would know of, *e.g.*, protease inhibitors or classes of other compounds which may be identified by contacting NT2N cells with such classes of agents and measuring levels of amyloid β peptides formed in the endoplasmic reticulum of said cells. Further, one of skill would know of routine cell-based screening protocols and reagents used in the identification of agents that modify the levels of amyloid β peptides formed in the endoplasmic reticulum.

Moreover, the courts have recognized that while a specification may lack examples of specific dosages, the application is considered enabled to one skilled in the art if the agent has certain pharmacolcgical properties (*e.g.*, the ability to inhibit the processing of amyloid precursor protein to amyloid β peptides found in neuritic plaques and vascular deposits) and possesses activity similar to known agents (*e.g.*, inhibitors of secretases). *In re Bundy*, 642 F.2d 430, 434, 209 USPQ 48, 51-52 (CCPA 1981).

The Examiner further suggests that Applicants' arguments regarding the Brinton et al. and Roses references cited by the Examiner in the previous Office Action (Paper No. 18, 06 November 2002) were not found to be persuasive and that the references were intended to indicate the state of the art at the time the invention was made. The Examiner suggests that these references indicate that Alzheimer's disease is recalcitrant to treatment, that there is no cure for Alzheimer's disease, and that only recently have therapeutic strategies emerged.

As indicated *supra*, claim 4 of the present invention is directed to a method of inhibiting the processing of amyloid precursor protein into amyloid β peptides found in neuritic plaques and vascular deposits which are signs of Alzheimer's disease.

Brinton et al. teach agents for preventing Alzheimer's disease such as the protective effects of 17 β-estradiol on neurons against oxidative damage induced by beta amyloid and other oxidants; anti-inflammatory therapy inhibition of Aβ activation of RAGE in both microglia and neurons to thereby block the self-perpetuating cycle of inflammatory reactions that induce

oxidative damage to neurons; and antioxidant therapy in combating oxidative damage. Brinton et al. further teach agents for treating Alzheimer's disease which include cholinergic agents for increasing levels of the neurotransmitter acetylcholine to improve cognitive performance and nerve growth factor to protect cholinergic neurons. Overall, Brinton et al. focus on the prevention of oxidative damage and the improvement of cognitive performance and are silent to the state of the art of agents which inhibit the processing of amyloid precursor protein into amyloid β peptides found in neuritic plaques and vascular deposits associated with Alzheimer's disease.

Roses teaches the various factors involved in the development of Alzheimer's disease subtypes and that a common effective treatment for Alzheimer's may not work for all patients, especially those with rare mutational forms of the disease. While Roses comments on the general state of mutational forms of Alzheimer's phenotypes, the context of Roses is biased toward understanding the application of pharmacogenetics to improve drug development and delivery of medicines. Like Brinton et al., Roses offers no teachings pertaining to inhibiting amyloid precursor processing. Thus, upon reading these references, the skilled artisan would have little understanding of the state of the art or the predictability of inhibiting the processing of amyloid precursor protein into amyloid β peptides found in neuritic plaques and vascular deposits that accumulate in brains of patients with Alzheimer's disease. Thus, these references do not address the claimed invention. Accordingly, withdrawal of these rejections under 35 U.S.C. § 112, first paragraph, is therefore respectfully requested.

III. Conclusion

The Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,

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